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Omalizumab, when to discontinue?

1/19/2011

Q. In patients that have had great success with the treatment of Xolair, is there a point to discontinue use of Xolair?

A. Thank you for your recent inquiry. Your question is certainly an important one, but to the best of my knowledge there are no well-established indices to help us decide when and if omalizumab therapy can be discontinued. But Dr. Robert Lanier has personally looked at this issue, and has published a great deal on the use of omalizumab. I am going to ask Dr. Lanier to share his thoughts with us in this regard because he is more knowledgeable in this area than I. When I hear from Dr. Lanier, I will forward his response to you.

Thank you again for your inquiry.

Sincerely,
Phil Lieberman, M.D.

Below is the response we received from Dr. Robert Lanier. Thank you again for your inquiry, and we hope this response is helpful to you.

Sincerely,
Phil Lieberman, M.D.

BACKGROUND: The situation is similar to the question how long do you continue allergy shots? In my mind - both Xolair and SCIT immunization efforts are based on clinical experience without any A or even B evidence, and probably have as variables with both time and dose.

OTHER EXPERIENCE: My goal has always been minimalist. I do one 100 shots for allergy at maintenance level at practice parameter doses and discontinue as a trial-re-institute with issues. This was a Wilford Hall military protocol I developed and continued in private practice (they are more variable now). I count these shots down and give people a realistic goal for completion similar to what a student does with piano or college - it''s a function of time and credits for graduation. As a result of entrance careful choice and this contractual thought, my completion rate for immunotherapy hovers at 82%.... a fairly remarkable figure if true, you would have to agree. I think my remission rate is comparable, but that''s really smoke and mirrors a conclusion reached as patients move on, and the absence of records requests fro other allergists.

XOLAIR EXPERIENCE With Xolair, I have pursued a similar time pattern limitation of two years thinking that is the minimal time frame to achieve immune learning. I now have 48 women who have completed this for a minimum of two years off. I had to put two back on for superstition (they panicked the first week), the rest seem tons better with minimal continuing asthma meds (I am happy with low dose ICS or medium dose ICS - I have never cured anybody in 42 years). I am doing what is historically referred to as the Babbage delima - the person [Charles Babbage] who developed the original computer called a difference engine in the 1860''s but was never able to complete the project

because he kept modifying it without a finished product. Every time I get ready to submit the manuscript, I find there is a loophole and modify the parameters. I have three Chinese post grads who are furious with me - they want their data analysis done while they visited published.

The tendency to continue this drug is strong and seductive, even in the face of no clinical response. My reps beg me not to do this. (In Florida two years ago, a patient was discontinued from Xolair and subsequently died a month later. The doctor had attended a conference where I recounted my practice. A flurry of intercompany rep emails across the country warned against the Lanier Maneuver of dis-contiuation.)

THE REAL ISSUE My concern is an old saw that the companies fear - no one really knows how Xolair works. The drug was approved prematurely without a response profile and now there is no incentive to build it. The mechanism of action proposed, is a compilation of the apparent and transient effects of Xolair (reduction of free IgE receptor down regulation etc) but the central mechanism in my mind has yet to be elucidated. Until it is, the length of treatment is entirely arbitrary and philosophical. The limitation research on my part, is to make this less than a lifetime treatment which builds financial barriers to utilization in anyone as manifest by the decision of the NICE review of the British Health System which precludes even a short trial. That will happen in this country if we go forward with the current medical legislation - we have to profile this drug and find an end point. I have some patients on this drug for 8 years as they were in original trials and got compassionate drug until approval. I follow them carefully and regularly. A number still have flaming positive skin tests by the way.

I believe there is much ignorance about drug effect of many categories of drugs - Xolair is no exception. I discontinue at two years with full intent of re-institution if there is deterioriation. In the interest of fair balance science, I do refer you to the work of Slavin who suggests that there is no basis for withdrawal. I also suggest this was a sponsored study (IMUS grants for Genentech sponsored studies are done only when it fits brand advancement by written policy - I know - I have had 3 investigator initiated grants turned down for this reason - two of which addressed this very issue) with a relatively small thesis that an increase in free IgE will cause exacerbation. My retort is to name one disease that is caused by free IgE.

abstract below:
J Allergy Clin Immunol. 2009 Jan;123(1):107-113.e3.
Asthma symptom re-emergence after omalizumab withdrawal correlates well with increasing IgE and decreasing pharmacokinetic concentrations.
Slavin RG, Ferioli C, Tannenbaum SJ, Martin C, Blogg M, Lowe PJ.
St Louis University School of Medicine, St Louis, MO, USA.
Comment in:
J Allergy Clin Immunol. 2009 Jan;123(1):114-5.
Abstract
BACKGROUND: Physicians have questioned whether omalizumab can be discontinued or the dose reduced after clinical improvement is seen in patients with severe asthma.
OBJECTIVES: To examine the relationships among omalizumab, free IgE, and clinical outcomes in a randomized, placebo-controlled trial in patients with severe persistent allergic asthma following a posology based on pretreatment total IgE and body weight.
METHODS: A pharmacokinetic-pharmacodynamic binding model was used to calculate free IgE, omalizumab, and total IgE concentrations during the 28-week treatment and 16-week follow-up of the INvestigation of Omalizumab in seVere Asthma TrEatment (INNOVATE) study. These were plotted against the mean changes in the total asthma symptom score, morning peak expiratory flow, and rescue medication use for physician-defined treatment responders and nonresponders.
RESULTS: The model accurately fitted omalizumab and free and total IgE, allowing

reconstruction of the entire time course for each patient. Free IgE was rapidly suppressed below the 50 ng/mL (20.8 IU/mL) target, although there was a notable period before clinical measures stabilized. After treatment cessation, free IgE and omalizumab returned toward baseline and, after a delay, asthma symptoms re-emerged. Model-derived omalizumab and free IgE concentrations correlated well with changes in clinical outcomes, particularly in omalizumab-treated responders. Asthma symptoms exhibited different correlations during response onset compared with response offset (hysteresis), indicative of physiological time delays between changes in IgE levels and pulmonary function.
CONCLUSION: Omalizumab and free IgE correlated well with clinical symptoms. Reducing omalizumab doses below those in the dosing table cannot be recommended; the resulting increase in free IgE would cause a deterioration in asthma control.

Bob Lanier

Key Words: omalizumab, asthma, Xolair

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